Cepheid

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Memorandum

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To: Dockets Management Branch (HFA-305)
Food and Drug Administration
Reference Docket No. 00N-1394

From: Bill McMillan, Director of Biotechnology
Cepheid

Date: 11Aug00

Subject: Submittal of Written Comments for Public Workshop, August 14-15, 2000. CLIA Requirements

Statement from Cepheid:

"New nucleic acid-based analytical reagent systems have been recently developed by various groups which we now believe can challenge the relevance of certain current CLIA regulations regarding the use of external controls.

Cepheid is developing a system called the GeneXpert PCR Cartridge System that is intended for use in both the laboratory and at the point of care. It is comprised of an instrument and a single-use, disposable cartridge, and can be designed for both moderate complexity and CLIA-waived applications. The cartridge contains all sample preparation and assay-specific reagents, sealed waste chamber, and an integrated PCR reaction tube that is used for multiplex real-time, homogeneous fluorescence PCR. Specimen preparation and analysis are completely automated. The PCR reagent incorporates molecular beacons probes. The PCR reaction is continuously monitored by the instrument through optical windows located in the reaction tube. Since the cartridge is never opened during or after processing, all liquids remain sealed in the cartridge. Amplicon contamination of the laboratory or POCT environment is completely prevented.

For current PCR-based analyses, external negative and positive controls can never verify the performance of the reagents in reaction mixture of the test unknown itself. They can only verify the performance of the reagents in a batch. We believe that POCT applications must have totally internally controlled schemes to assure a valid, clinically-relevant result and to be cost-effective in terms of cartridge design and complexity. Based on existing technical feasibility data, we believe a molecular beacons-based multiplex reagent system containing an internal control and a thermal-optical probes check will together verify the analytical performance of the reagent and instrument for each and every specimen. This capability is completely unavailable in any other kind of analytical reagent system. Furthermore, Cepheid has the capability to assure that reagents are manufactured and assembled into sealed cartridges using processes validated to be free of contaminating target or amplicons.

We strongly urge that the requirements for external controls for moderate complexity devices be reconsidered, particularly where these new types of reagent systems can be applied."

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